DEC 11 3 2017

<110> M&E Biotech A/S

<120> Method for down-regulating GDF-8 activity

<130> 3631-0117P

<140> 09/620,586

<141> 2000-07-20

<160> 24

<170> PatentIn Ver. 2.1

<210> 1

<211> 375

<212> PRT

<213> Homo sapiens

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Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Lys

Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys

230

260

Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val

235

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 Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
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                                        315
 Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
                325
                                    330
 Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
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<212> PRT
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Gln Asn Thr Lys Ser Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu
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Ser Lys Leu Arg Leu Glu Gln Ala Pro Asn Ile Ser Arg Asp Val Ile
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Lys Gln Leu Leu Pro Lys Ala Pro Pro Leu Gln Glu Leu Ile Asp Gln
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Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp
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Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser
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Asp Phe Leu Val Gln Met Glu Gly Lys Pro Lys Cys Cys Phe Phe Lys
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Phe Ser Ser Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp
                       135
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Ile Tyr Leu Arg Gln Val Gln Lys Pro Thr Thr Val Phe Val Gln Ile
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Leu Arg Leu Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile
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Arg Ser Leu Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser
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Ile Asp Val Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser
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Asn Leu Gly Ile Glu Ile Lys Ala Phe Asp Glu Asn Gly Arg Asp Leu
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Ala Val Thr Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu
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Glu Val Arg Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly
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Leu Asp Cys Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro
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Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro
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Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe 295 Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg 310 315 Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn 325 330 Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro 345 Ala Met Val Val Asp Arg Cys Gly Cys Ser

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305 310 315 Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala 325 330 Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr 340 345 Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ala Met Val 360 Val Asp Arg Cys Gly Cys Ser <210> 4 <211> 376 <212> PRT <213> Mus musculus <400> 4 Met Met Gln Lys Leu Gln Met Tyr Val Tyr Ile Tyr Leu Phe Met Leu 10 Ile Ala Ala Gly Pro Val Asp Leu Asn Glu Gly Ser Glu Arg Glu Glu Asn Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Ala Trp Arg Gln Asn 40 Thr Arg Tyr Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys Leu Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Ala Ile Arg Gln 70 . 75 Leu Leu Pro Arg Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp 85 90 Val Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr 105 His Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe 120 125 Leu Met Gln Ala Asp Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser 135 140 Ser Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp Ile Tyr 150 155 Leu Arg Pro Val Lys Thr Pro Thr Thr Val Phe Val Gln Ile Leu Arg 165 170 Leu Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser 180 185 190 Leu Lys Leu Asp Met Ser Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp 200 Val Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu 215 Gly Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val 235 Thr Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val 250 Lys Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp 265 Cys Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr 280 285 Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg 295 Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln

315

Lys Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser 325 330 Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu 345 Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ala Met 360 Val Val Asp Arg Cys Gly Cys Ser

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<400> 5

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330

Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr 340. 345 350

Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Gly Met Val 355 360 365

Val Asp Arg Cys Gly Cys Ser 370

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340 345 Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ala Met 360 Val Val Asp Arg Cys Gly Cys Ser 370 <210> 8 <211> 375 <212> PRT <213> Sus scrofa Met Gln Lys Leu Gln Ile Tyr Val Tyr Ile Tyr Leu Phe Met Leu Ile 10 Val Ala Gly Pro Val Asp Leu Asn Glu Asn Ser Glu Gln Lys Glu Asn 25 Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Met Trp Arg Gln Asn Thr 40 Lys Ser Ser Arg Leu Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys Leu 55 Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Ala Ile Arg Gln Leu 70 75 Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val 90 Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His 100 105 Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Leu Leu 120 125 Met Gln Val Glu Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser Ser 135 140 Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp Ile Tyr Leu 150 155 Arg Pro Val Lys Thr Pro Thr Thr Val Phe Val Gln Ile Leu Arg Leu 165 170 175 Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser Leu 185 190 Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp Val 200 Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly 215 Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val Thr 230 235 Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Lys 245 250 Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys 265 Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val 280 Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr 295 Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys 310 315 Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala 325 330 Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr

345

Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ala Met Val 355 . 360 365

Val Asp Arg Cys Gly Cys Ser 370 375

<210> 9 <211> 374 <212> PRT <213> Danio rerio <400> 9 Met His Phe Thr Gln Val Leu Ile Ser Leu Ser Val Leu Ile Ala Cys 10 Gly Pro Val Gly Tyr Gly Asp Ile Thr Ala His Gln Gln Pro Ser Thr 25 Ala Thr Glu Glu Ser Glu Leu Cys Ser Thr Cys Glu Phe Arg Gln His 40 Ser Lys Leu Met Arg Leu His Ala Ile Lys Ser Gln Ile Leu Ser Lys 55 Leu Arg Leu Lys Gln Ala Pro Asn Ile Ser Arg Asp Val Val Lys Gln 70 75 Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln Leu Leu Asp Gln Tyr Asp 90 Val Leu Gly Asp Asp Ser Lys Asp Gly Ala Val Glu Glu Asp Asp Glu 100 105 His Ala Thr Thr Glu Thr Ile Met Thr Met Ala Thr Glu Pro Asp Pro 120 125 Ile Val Gln Val Asp Arg Lys Pro Lys Cys Cys Phe Phe Ser Phe Ser 135 140 Pro Lys Ile Gln Ala Asn Arg Ile Val Arg Ala Gln Leu Trp Val His 150 155 Leu Arg Pro Ala Glu Glu Ala Thr Thr Val Phe Leu Gln Ile Ser Arg 165 170 Leu Met Pro Val Lys Asp Gly Gly Arg His Arg Ile Arg Ser Leu Lys 185 Ile Asp Val Asn Ala Gly Val Thr Ser Trp Gln Ser Ile Asp Val Lys 195 200 Gln Val Leu Thr Val Trp Leu Lys Gln Pro Glu Thr Asn Arg Gly Ile 215 Glu Ile Asn Ala Tyr Asp Ala Lys Gly Asn Asp Leu Ala Val Thr Ser 230 235 Thr Glu Thr Gly Glu Asp Gly Leu Leu Pro Phe Met Glu Val Lys Ile 250 245 Ser Glu Gly Pro Lys Arg Ile Arg Arg Asp Ser Gly Leu Asp Cys Asp 265 270 Glu Asn Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val Asp 280 Phe Glu Asp Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr Lys 295 Ala Asn Tyr Cys Ser Gly Glu Cys Asp Tyr Met Tyr Leu Gln Lys Tyr

Pro His Thr His Leu Val Asn Lys Ala Ser Pro Arg Gly Thr Ala Gly

Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr Phe 340 345 350 Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ser Met Val Val

310

325

330

Asp Arg Cys Gly Cys Ser 370

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<213> Papio hamadryas

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Val Asp Arg Cys Gly Cys Ser
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Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
                             40
Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
                         55
Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
                                         75
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Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly
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                                     90
Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
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                                 25
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Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
                             40
                                                  45
Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
                         55
Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
                     70
                                         75
Pro Ile Asn Met Leu Tyr Phe Asn Gly Glu Gly Gln Ile Ile Tyr Gly
                                     90
                 85
Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
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Phe Asn Asn Phe Thr Val Ser Phe Trp Leu Arg Val Pro Lys Val Ser
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Ala Ser His Leu Glu
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Arg Gln Tyr Ile Lys Ala Asn Ser Lys Phe Ile Gly Ile Thr Glu Leu
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Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
                             40
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Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
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Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
                     70
                                         75
Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly
                85
                                     90
Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
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<222> (67)..(109)
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Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile
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                                 25
Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
                             40
Phe Val Phe Gln Tyr Ile Lys Ala Asn Ser Lys Phe Ile Gly Ile Thr
Glu Leu Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
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Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly
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Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser

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Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
                             40
Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
                         55
Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
                                         75
Pro Ile Gln Tyr Ile Lys Ala Asn Ser Lys Phe Ile Gly Ile Thr Glu
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Leu Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
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<223> Lys Glu or Glu Gly
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Arg Tyr Pro Leu Phe Asn Asn Phe Thr Val Ser Phe Trp Leu Arg Val
                                 25
Pro Lys Val Ser Ala Ser His Leu Glu Tyr Cys Ser Gly Glu Cys Glu
                             40
                                                  45
Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
                         55
Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
                                         75
                     70
Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly
                                      90
Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
<210> 19
<211> 109
<212> PRT
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Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile
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Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
                             40
Phe Asn Asn Phe Thr Val Ser Phe Trp Leu Arg Val Pro Lys Val Ser
                         55
Ala Ser His Leu Glu Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
                                         75
Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly
                85
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Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
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Asp Phe Gly Leu Asp Cys Asp Glu His Ser Thr Glu Ser Arg Cys Cys
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Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile
             20
                                  25
Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
                         55
Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Phe Asn
                     70
                                         75
Asn Phe Thr Val Ser Phe Trp Leu Arg Val Pro Lys Val Ser Ala Ser
His Leu Glu Ala Met Val Val Asp Arg Cys Gly Cys Ser
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Asp Phe Gly Leu Asp Cys Asp Glu His Ser Thr Glu Ser Arg Cys Cys
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Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile
Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
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Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
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Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
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Pro Ile Asn Phe Asn Asn Phe Thr Val Ser Phe Trp Leu Arg Val Pro
Lys Val Ser Ala Ser His Leu Glu Arg Cys Gly Cys Ser
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Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
         35
                             40
Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
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65
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Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly
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Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser Gln Tyr Ile
                                105
Lys Ala Asn Ser Lys Phe Ile Gly Ile Thr Glu Leu Phe Asn Asn Phe
        115
                            120
                                                125
Thr Val Ser Phe Trp Leu Arg Val Pro Lys Val Ser Ala Ser His Leu
                        135
                                            140
Glu Asp Phe Gly Leu Asp Cys Asp Glu His Ser Thr Glu Ser Arg Cys
                    150
                                        155
Cys Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp
                165
                                    170
Ile Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys
                                185
Glu Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln
                            200
Ala Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met
                        215
Ser Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr
225
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Gly Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
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Asn Asn Phe Thr Val Ser Phe Trp Leu Arg Val Pro Lys Val Ser Ala
Ser His Leu Glu Gln Tyr Ile Lys Ala Asn Ser Lys Phe Ile Gly Ile
                            40
Thr Glu Leu Asp Phe Gly Leu Asp Cys Asp Glu His Ser Thr Glu Ser
                                            60
Arg Cys Cys Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp
                    70
                                        75
Asp Trp Ile Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly
                                    90
Glu Cys Glu Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val
           100
                                105
His Gln Ala Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr
                            120
                                               125
Lys Met Ser Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile
                      135
                                           140
Ile Tyr Gly Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
                                        155
<210> 24
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<223> PADRE Peptide
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Ala Lys Phe Val Ala Ala Trp Thr Leu Lys Ala Ala Ala
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